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The Preparation of the Di-Substituted Formamidines and the Reactions of Di-p-Xylyl-Formamidine.

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DIPHENYL formamidine, $C_6H_5N{:}CHNHC_6H_5$, has been prepared by various methods, one of the simplest of which was suggested by Weith (*1*) and studied more in detail many years later by Shoesmith and Haldane (*2*). Their description is as follows: "Forty grams (1 mole) of 80 per cent formic acid were mixed with 160 grams (2.4 moles) of aniline. The water which was present in the original acid, together with that produced in the reaction, was distilled away through a fractionating column. The head of the column was fitted with a device for trapping the water as soon as it reached the top. After four hours gentle boil the temperature was raised until 60 cc. of aniline had distilled over. The residual diphenyl formamidine solidified on cooling, and after recrystallization from alcohol melted at 137 degrees (yield 63 grams)."

In our own experiments the pyrex flask was fitted with a 20-inch glass tube (3/8 in. diam.) the upper end of which bent so as to connect with an ordinary water condenser. When the contents of the flask were boiled gently water vapor was given off and condensed, carrying only a few drops of aniline with it. It was usually found necessary to continue the heating for from 8 to 12 hours before the reaction mixture solidified. This product was then transferred to a distilling flask and 60 to 70 cc. of aniline distilled over. The residue was purified by treatment with gasoline or absolute alcohol. The dipthenyl formamidine obtained was somewhat colored, but of good quality. However, the yields were not very satisfactory, ranging in nine trials from 33 to 50 grams, with an average of 37 grams.

1. Ber. 9, 454 (1876).
2. J. Chem. Soc. 123, 3705 (1923).

DI-p-TOLYL-FORMAMIDINE, $C_7H_7NCHNHC_7H_7$.

A mixture of formic acid (46 gms.) and p-toluidine (179 gms.) was heated under like conditions for 12 hours and then p-toluidine (60 cc.) was distilled from the reaction mixture. On working up the residual product a yield of from 33 to 40 grams of the pure formamidine was obtained.

DI-o-TOLYL-FORMAMIDINE, $C_7H_7NCHNHC_7H_7$.

The same proportions and procedure were used as with p-toluidine, but the yield is still more unsatisfactory, since only 23 grams of pure di-o-tolyl formamidine were obtained from 179 grams of o-toluidine.

The foregoing results show that the phenyl o- and p-tolyl formamidines can be synthesized by this method, but it is not practical except with the cheaper and more available aromatic amines.

The most satisfactory reagent for the preparation of these di-substituted formamidines is orthoformic ester. This gives clean products and almost quantitative yields, and has been used in this laboratory with a wide variety of aromatic amines. The procedure is simple, since it consists in heating the ester (1 mole) and the amine (2 moles) at 100 or 120 degrees for one to two hours and purifying the product from gasoline or gasoline and penzene, $HC(OC_2H_5)_3 + 2RNH_2 = RNCHNHR + 3C_2H_5OH$.

DI-p-XYLYL-FORMAMIDINE, $(CH_3)_2C_6H_3NH\text{-}CH{:}NC_6H_3(CH_3)_2$.

This was readily prepared in good yield by heating orthoformic ester (1 mole) and p-xylidine (1-amino-2-5-dimethyl-benzene) (2 moles) for two hours at 20 degrees in an oil bath. The solid product was washed on the filter with a little gasoline and purified by crystallization from benzene. It then melted at 155 degrees.

Analyses: Calcd. for $C_{17}H_{20}N_2$: N, 11.11. Found: 10.71.

REACTIONS OF THIS FORMAMIDINE.

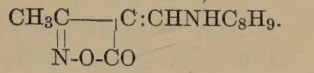
In a previous series of papers it has been shown that the methylene hydrogen, both in open chain compounds such as aceto acetic ester and in heterocyclic rings such as the isoxazolones, could be readily replaced by the complex $>CHNHR$, thus giving a carbon—carbon synthesis, as follows:

$$X_2CH_2 + RN{:}CHNHR = X_2C{:}CHNHR.$$

Various syntheses were carried out using the xylyl formamidine in order to ascertain whether the presence of methyl groups at positions 2 and 5 in the amine would affect the general course of the re-

action. The following results indicate that the syntheses proceeded normally:

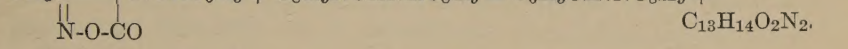
3-METHYL-4-p-XYLYL-AMINO-METHYLENE-5-ISOXAZOLONE,



A molar mixture of di-p-xylyl formamidine and 3-methyl-4-benzal-isoxazolone in a little xylene was heated in an oil bath for a few minutes at 150 degrees and then the temperature was lowered to 115-120 degrees and kept there for two hours. After evaporating the xylene from the mixture, the reaction product was dissolved in hot alcohol, from which the above compound crystalizes in dark yellow needles, melting at 193 degrees, while the benzal-p-xylidine remains in solution.

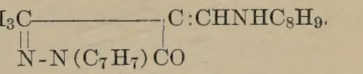
Analyses: Calcd. for $C_{13}H_{14}O_2N_2$: N, 12.17. Found: 12.18.

It will be noticed that in this case an unusual type of reaction occurs, viz., the replacement of a doubly bound benzal grouping by the xylyl amino methylene complex:



In the case of the benzal compound such replacement takes place easily and smoothly which in the unsubstituted isoxazolones the yield is mainly tar.

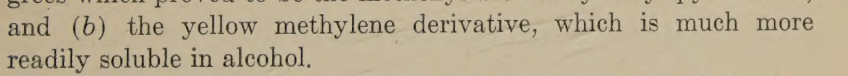
1-p-TOLYL-3-METHYL-4-p-XYLYL-AMINO-METHYLENE-PYRAZOLONE,



The formamidine and p-tolyl-methyl pyrazolone were heated at 120-130 degrees for two hours, with the formation of two products: (*a*) an orange red difficultly soluble compound melting at 249 degrees which proved to be the methenyl-bis-methyl tolyl pyrazolone; and (*b*) the yellow methylene derivative, which is much more readily soluble in alcohol.

Analyses: Calcd. for $C_{20}H_{21}ON_3$: N, 13.16. Found: 12.94.

The presence of the bis-pyrazolone is due to the action of a second mole of the pyrazolone upon the amino methylene compound as follows:



p-XYLYL-AMINO-METHYLENE-CYANACETIC ETHYL ESTER,

$$\begin{array}{l} CN\text{-}C{:}CHNHC_8H_9. \\ \quad\;\; | \\ \quad\;\; COOC_2H_5 \end{array}$$

This was synthesized when a mixture of ethyl cyanacetate and the formamidine was heated at 120 degrees for three hours. It crystallized from alcohol in colorless needles, which melt at 153 degrees.

Analyses: Calcd. for $C_{14}H_{16}O_2N_2$: N, 11.47. Found: 11.39.

p-XYLYL-AMINO-METHYLENE-ACETYL-ACETONE,

$$(CH_3CO)_2C{:}CHNHC_8H_9.$$

The methylene hydrogen in the acetyl-acetone was readily replaced on heating with the formamidine at 130 degrees for three hours,

$$(CH_3CO)_2CH_2 + C_8H_9NCHNHC_8H_9 = C_8H_9NH_2 + C_{14}H_{17}O_2N$$

It is easily soluble in alcohol, from which it separated in colorless needles melting at 125 degrees.

Analyses: Calcd. for $C_{14}H_{17}O_2N$. N, 6.06. Found: 5.77.

p-XYLYL-AMINO-METHYLENE-ACETO ACET-p-XYLIDIDE,

$$\begin{array}{l} CH_3COC{:}CHNHC_8H_9 \\ \quad\;\; | \\ \quad\;\; CONHC_8H_9 \end{array}$$

When the di-xylyl formamidine and ethyl acetoacetate are allowed to react at 110-120 degrees for two hours, not only is the methylene hydrogen replaced, but the xylidine set free combines with the carbethoxy group, yielding alcohol and the acid amide derivative. This illustrates the greater reactivity of the $COOC_2H_5$ grouping in acetoacetic ester as compared with the preceeding ethyl cyanacetate where no such replacement occurred. The new compound melted at 140 degrees when crystallized from alcohol.

Analyses: Calcd. for $C_{21}H_{24}O_2N_2$: N, 8.33. Found: 7.99.

p-XYLYL-AMINO-METHYLENE-BENZOYL-ACETO-p-XYLIDIDE,

$$\begin{array}{l} C_6H_5COC{:}CHNHC_8H_9. \\ \quad\;\; | \\ \quad\;\; CONHC_8H_9 \end{array}$$

This was the main product when the amidine was heated with ethyl benzoylacetate for two hours at 110 degrees. It was difficultly soluble in alcohol and when crystallized from glacial acetic acid melted at 182 degrees.

Analyses: Calcd. for $C_{26}H_{26}O_2N_2$: N, 7.03. Found: 6.71.

A small amount of a compound melting at 130 degrees was isolated, but not enough for analysis. This was doubtless the ethyl ester of the amino-methylene derivative.

The p-Xylidides of benzoylacetic ester and acetoacetic ester were formed in good yields when the esters were heated with p-xylidine for three hours at 115-130 degrees. They were purified by crystallizing from alcohol.

BENZOYL-ACETO-p-XYLIDIDE, $C_6H_5COCH_2CONHC_8H_9$.
M. P. 142 DEGREES.

Analyses: Calcd. for $C_{17}H_{17}O_2N$: N, 5.24. Found: 5.30.

ACETYL-ACETO-p-XYLIDIDE, $CH_3CONHCONHC_8H_9$.
M. P. 98 DEGREES.

Analyses: Calcd. for $C_{12}H_{15}O_2N$: N, 6.82. Found: 6.83.

ACTION OF BROMINE UPON DI-p-XYLYL FORMAMIDINE.

Bromine (1 mole) acted upon the formamidine in chloroform solution, giving a yellow solid, melting at 162 degrees, which was evidently the HBr salt of a monobromo di-p-xylyl formamidine, $C_8H_9NCHC_8H_8Br.HBr$.

Analyses: Calcd. for $C_{17}H_{18}N_2Br_2$: N, 6.83. Found: 6.56.

SUMMARY.

(*a*) A study has been made of the preparation of di-phenyl, di-o-tolyl and di-p-tolyl formamidine from the amine and formic acid. The method, while feasible, gives unsatisfactory yields.

(*b*) Di-p-xylyl formamidine has been synthesized, as well as its condensation products, with a number of compounds containing methylene hydrogen.